Biomedicine: 2024; 44(2):184-189 *April-June 2024*
Review Article

Physiological Aspects Responsible For Mucormycosis Outbreak

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(Received : 09.05.2024 Revised : 06.07.2024 Accepted : 10.07.2024)

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ABSTRACT

Here in this article, we provide an overview of related terminologies, physiological factors and their mechanisms responsible for outbreak of mucormycosis. Mucormycosis indicates diseases caused by many non-septate filamentous fungal species earlier designated under mucorales and entomophthorales. Being present everywhere in soil, mucormycosis is exceptionally prevalent in waterlogged soil, putrescent plants and foods, excreta of birds and animals, air & water surrounding the buildings. Diverse set of exposures such as rise in the incidence of diabetes, immunosuppressant use and trial prophylaxis among immune compromised patients has been linked with the advent of mucormycosis outbreaks.

Keywords: Covid 19, Mucormycosis outbreak, Immunosuppression, Emergence, Hyperglycemia

INTRODUCTION

Before pandemic bashed the world, mucormycosis was reported as the second most common invasive fungal infection, associated with high illness and death rates among immunocompromised persons and India accounted for the world's largest burden of the same. Studies related to mucormycosis outbreak initially limited to nose and sinuses subsequently involving orbital and cerebral region due to widespread invasion among patients treated for COVID-19 were reported . However, data related to critical factors and the mechanisms responsible for mucormycosis outbreak are limited (1). Thus, in this article, we intent to discuss the terminologies and various possible mechanisms related to mucormycosis and its outbreak which would help curb high prevalence rates.

The blanket term Mucormycosis indicates diseases caused by many non-septate filamentous fungal species earlier designated under mucorales and entomophthorales. It is considered as an acute potentially fatal opportunistic infection caused by diverse group of fungi that belonged to subphylum Mucoromycotina and Entomopthoromycotina (2). Fur Binger, in 1876 first reported the disease in haemorrhagic infarct of lung cancer patient. Later, Arnold Paltauf , in 1885 confirmed the first case of disseminated Mucormycosis as “Mycosis mucorina”, designated later as Mucormycosis by Baker, in the year 1957 for an aggressive infection caused by Rhizopus (3).

These Saprotrophic fungi being present everywhere in soil is mostly prevalent in waterlogged soils, putrescent plants and eatables, excreta of birds and animals, water and air around the buildings. Some inhabit the animals, plants, and other fungi as parasites. In humans, the infection is acquired mainly through airborne fungal spores (4). Due to emerging pathogenic organisms resulting in fatal consequences among patients with an impaired immune system, recent understanding has changed the perspective though earlier recognized as laboratory contaminants (5). Due to technical issues encountered in collection of samples from deep tissues and less sensitive diagnostic tests, many cases of mucormycosis remain undiagnosed and the true

incidence/prevalence is often considered to be more than what is visible. According to Leading International Fungal Education (LIFE) estimates, the annual prevalence of mucormycosis is about 910,000 globally. Mucormycosis is believed to mainly affect population with multiple chronic conditions like diabetes, neutropenia, iron overload, deferoxamine therapy, renal failure, protein-calorie malnutrition, those with weakened host defence and/or with increased serum iron availability (4, 5). The condition which was formerly almost always community acquired has rapidly evolved as a nosocomial infection in those individuals with malignancy, long-term treatment with corticosteroids and organ /stem cell transplantation(6).Iatrogenic immunosuppression or healthcare-associated procedures including antifungal prophylaxis, use of contaminated bandages or medication patches, intravenous catheters, unsterilized tongue depressors have been considered to be associated with nosocomial mucormycosis. Added to this, air contamination has also been proved to be a source of infection (7).

Mucormycosis outbreak

When more number of cases related to a disease than expected is recorded in a distinct location over a particular time period, the situation is referred as an outbreak (8). Multiple factors such as surge in diabetic cases, immunosuppressant use and management of immune compromised patients have been shown to be connected with unfolding of mucormycosis outbreak (9). It is believed that initial presentations of infections provide clue to the site of entry of spores. Few examples to mention include peritoneal dialysis leading to peritonitis and use of bladder catheter linked to cystitis. In case of cutaneous infections, skin sites exposed to contaminated products including bandages, adhesives, and fabric were thought to be the cause for initial lesions and pulmonary infections were linked with exposure to airborne spores. Nevertheless, it is proven that a single source may lead to infections with multiple presentations among which pulmonary and cutaneous presentations linked to use of contaminated linens and negative pressure room amongst immune compromised patients requires special mention (10). In vitro studies also suggest possibility of decreased innate host defence against R. oryzae and other members of the Mucorales though differential interspecies susceptibility patterns to host responses exists when compared to other usual fungi, such as Candida albicans /Aspergillus fumigatus.

Possible physiological factors associated with mucormycosis outbreak.

1. Hyperglycaemia: Since low pH caused by acidosis and carbohydrate rich environment is considered as an excellent media for mucor spores to germinate, Diabetic individuals are believed to be more susceptible to mucormycosis more so in the setting of ketoacidosis . Other possible explanations include impaired phagocytic motility, reduced oxidative and non-oxidative killing of the causal pathogen. Metabolic reprogramming has been known to be associated with impaired function of phagocytes. Proponents suggest use glycolytic pathway instead of Kreb'scycle and mitochondrial electron transport chain for energy requirement by activated macrophages to support immunological action, amino acids, ribosomes and NADPH synthesis considered essential for the production of DNA, several inflammatory mediators and also reactive oxygen species that are known to be dependent on glycolytic pathway. Since glycolytic pathway is impaired in diabetic individuals, the classical functioning of macrophages in response to pathogen is impaired. Further immune cell inflammatory response against mucormycetes is impaired by oxidative stress caused by hyperglycemia.

AGEs caused by chronic hyperglycemia lead to inter-linking of inflammatory crucial proteins and collagen forming tissues receptive to immunological dysregulation. Activation of RAGE (Receptor for AGE) manifested in a variety inflammatory cells results in

activation of numerous down signalling pathways which ultimately accelerate impairment of the inflammatory response (11). Pathological changes resulting in impaired inflammatory response against pathogen includes increase in serum Nitric Oxide (NO) induced by hyperglycemia, which in turn impairs neutrophil motility, production and release of innumerable inflammatory mediators such as Tumor Necrosis Factor -α , Interleukin -1β & Interleukin -6, expression of adhesion molecules like LFA-1 and ICAM-2 on neutrophils (12).

2. Mucormycosis and Covid 19: Emergence of COVID-19 during the later months of 2019 devastated human health & health care severely affecting the economy worldwide and cases of COVID-19-associated mucormycosis were reported in significant numbers from early 2021.India being second most affected country, patients witnessed fungal co infections like mucormycosis, aspergillosis and invasive candidiasis, during or after weeks or months of recovery. COVID-19 individuals with uncontrolled diabetes mellitus, diabetic ketoacidosis, immoderate glucocorticoid use, neutropenia for longer duration, malnutrition and other underlying immune compromised conditions were regarded as Individuals at risk of developing mucormycosis. Though the diagnosis appeared to be challenging due to paucity in clinical suspicion, delayed presentation, in availability of prompt diagnostic services resulted in under diagnosis of mucormycosis and worst prognosis in COVID-19 patients. Possible mechanisms suggested to have led to mucormycosis in individuals with COVID-19 on corticosteroid therapy include impaired bronchoalveolar macrophage migration, ingestion, and phagolysosome fusion. Endothelialitis, endothelial damage, thrombosis, and lymphopenia, reduction in CD4þ and CD8þ T-cell level due to Covid also has been proposed to predispose the individual to risk of secondary or opportunistic fungal infection (13).

3. Steroids and Mucormycosis: Steroids are known to cause immune suppression mainly through inhibition of NF-κB pathway, a transcription factor responsible for the formation of immunological mediators like Interleukins, cytokines, chemokines and adhesion molecules. It is also known to decrease the T cell mediated response against the pathogens by inducing apoptosis of T cells and formation of end products of inflammation like prostaglandins and leukotrienes (14). Steroids are believed to function mainly through interaction with glucocorticoid receptors, resulting in decreased expression of pro inflammatory cytokines such as tumour necrosis factor (TNF)-α, IL-1β, IL-6, IL-8, and IL-12 resulting in immune suppression (15).

4. Uncontrolled traditional preventive measures: Many individuals followed traditional preventive measures like repeated steaming, leading to destruction of the beneficial microbiome and virome present in the nasal mucosa leading to opportunistic fungal infection .Majority of population during Covid pandemic took Zn along with vitamins and other dietary supplements in an attempt to combat Covid 19 infection. Though Zinc is known to affect quite a few aspects related to immune system and is essential for normal development and functioning of cells involved in innate immunity, It is evident that inhibition of fungal growth in the body is linked with Zn deprivation and host cells employ zinc sequestration as a mechanism to hamper fungal development (16,17)

5. Seasonal variation and Mucormycosis: Emergence of Mucormycosis was also influenced by Climatic conditions such as seasonal variation, humidity, and ambient temperature .Though believed to be present throughout the year in the environment, a strong influence of seasonal variation on infection pattern is seen. Most infections confirmed to be widespread during the early times of dry and hot summer season, with peaks during the end of summer season due to and both high temperature and relative humidity. Also precipitation is low during this time (18).

6. Mucormycosis and Gut Microbiota: Inadervent usage of antibiotics, steroids, vitamins, and Zn, excessive steaming and so on has been linked with gut dysbiosis and nasal microbiomes. Well-developed and largest lymphoid immune organ, the Gut-associated lymphoid tissue (GALT) protects the host against various pathogens and infectious agents besides playing an important role in post-natal immunity.Colonial microbial symbionts that are close to external ambiance is known to modulate the barrier function, local and distal immune responses of the nasal mucosa (19).The host's physiological and pathological processes are modulated by microbiota through multiple mechanisms. The Gut microbiota cross react with the pulmonary microorganisms through gut-lung axis and thereby affect the immune system by regulating and influencing the host's susceptibility to respiratory infections (20). Effective functioning of the immune cells that are believed to be crucial for controlling microbial infections depend mainly on the interaction of mucorales-specific T-cells producing CD4+ and CD8+ with Gut microbiota (21). Nasal immune responses against viral, bacterial and fungal infections are mainly mediated by Nasal microbiota (22).Similar to other mucosal surfaces, commensals responsible for mucosal homeostasis and prevention of nasal infections are also colonized in the nasal tract (23). Staphylococcus epidermidis, important determinant for human nasal microbiome maturation, stimulates the synthesis of antimicrobial peptides in nasal epithelium (24). An immune component of mammalian mucosa-associated lymphoid tissue (MALT), Nasal- Oro nasopharynx-associated lymphoid tissue (NALT) bring forth additional protection to the nasal mucosal barrier (25).It is worth mentioning that the nasal microbiome acts as crucial factor for the development and maturation of MALT including alteration in IgA- and T cells-mediated adaptive immune responses.

7. Antibiotic Resistance and Mucormycosis: Latest studies have stressed on the prevalence of antibiotic resistance among bacteria causing secondary infections and exclusively health care associated candida resistance to antifungal drugs in India due to unrestrained use of antibiotics and antifungal drugs during Covid-19 pandemic (26, 27) Possible explanation to this would be gut microbiome dysbiosis caused by drugs prescribed during management of Covid pandemic. Further research must assess correlation of microbiome dysbiosis with drugs being used in Covid-19 in particular context to immune suppression and Mucormycosis.

8.Mucormycosis and Iron Overload: Hemosiderosis caused by immoderate usage of iron chelator, deferoxamine has considerably increased the incidence of invasive mucormycosis, linked with 80% mortality among these patients. Deferoxamine predisposes individuals to Rhizopus infection by acting as a siderophore, supplying earlier unavailable iron to the fungus though acting as an iron chelator with regard to the human host. Through intracellular transport, Rhizopus obtains iron from the iron deferoxamine complex which is likely to be mediated by high-affinity iron permeases. In the presence of acidosis, patients with diabetic ketoacidosis have increased levels of available serum iron and they release iron from binding proteins since acidosis temporarily disrupts the ability of transferrin to bind iron. This proton mediated dissociation of iron from transferring increases susceptibility of individuals with diabetic ketoacidosis to mucormycosis (28)

CONCLUSION

Though outbreaks of mucormycosis are rare, they are quite serious. In healthcare settings, outbreaks have been associated with use of contaminated instruments, linen and so on. Possible physiological factors associated with mucormycosis outbreak include uncontrolled Diabetes mellitus, inadvertent use of steroids, and unrestrained use of traditional preventive measures, seasonal variations, variations in gut microbiota, antibiotic resistance and iron overload.

CONFLICT OF INTEREST – None declared by authors.

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